EXHIBIT 12

Chronic traumatic encephalopathy and risk of suicide in former athletes

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ABSTRACT

Background In the initial autopsy case studies of chronic traumatic encephalopathy (CTE), some researchers have concluded that the proteinopathy associated with CTE is the underlying cause of suicidality and completed suicide in former athletes.

Methods A review of the literature on contact sports

and risk of completed suicide revealed only one epidemiological study with direct relevant data. **Results** There are no published cross-sectional, epidemiological or prospective studies showing a relation between contact sports and risk of suicide. One published epidemiological study suggests that retired National Football League players have lower rates of death by suicide than the general population. Outside of sports, there is a mature body of evidence suggesting that the causes of suicide are complex, multifactorial and difficult to predict in individual cases.

Conclusions Future research might establish a clear causal connection between the proteinopathy of CTE and suicide. At present, however, there is insufficient scientific evidence to conclude that there is a strong causal relationship between the presence of these proteinopathies and suicide in former athletes. Additional research is needed to determine the extent to which the neuropathology of CTE is a possible mediator or moderator variable associated with suicide.

INTRODUCTION

In recent years, there has been widespread and frequent media reporting of a possible connection between suicide and participation in contact sports, such as American football and ice hockey. The media has reported that between 2011 and 2013, six National Football League (NFL) players or former players have died by suicide. There have also been highly publicised cases involving professional hockey players. Through published autopsy case studies, suicide has been linked to chronic traumatic encephalopathy (CTE),^{1 2} and CTE has been linked to contact sports.^{3 4} CTE was originally described in boxers⁵ and a revised version of the neuropathology and neuropsychiatric syndrome has been described in the past few years by two research groups based on a series of autopsy cases.3 4 7-12 The modern version of CTE is considered a progressive neurodegenerative condition characterised by changes in personality, cognition and physical functioning. Until now, because CTE cannot be diagnosed in a living person, chronic psychiatric problems, drug misuse, aggression and suicidal behaviour have been linked to neuropathology only through postmortem case studies. 1 2 4 8 The microscopic neuropathology of CTE has been characterised as (1) an abundance of neurofibrillary inclusions in the form of neurofibrillary tangles, neuropil threads and glial tangles; (2) β -amyloid deposits; and (3) widespread TDP-43 proteinopathy. Therefore, by logical extension, it has been assumed that participation in contact sports results in concussions and subconcussive blows to the head and body, these injuries and blows cause neuropathological changes in the brain, these progressive neuropathological changes cause a neuropsychiatric disease years or decades after retirement from sports and a core clinical feature of this neuropsychiatric disease is personality change and suicide.

REVIEW

The rate of suicide in civilians¹³ and the military¹⁴ has increased in recent years, and people are now more likely to die by suicide than by motor vehicle accidents. 15 In civilians, researchers have reported that suicide rates have increased in dozens of countries in relation to the worldwide economic crisis. 16-18 Men are much more likely to complete suicide than women (27.3 vs 8.1/100 000 in the USA in 2010), and the rates of suicide in men and women were significantly higher in 2010 compared to 1999. 13 Men in their 50s had the greatest increase in suicide rates compared to other age groups, and white men (34.2/100 000 in 2010) are much more likely to complete suicide than African-American (11.4/100 000) or Hispanic men $(12.1/100\ 000^{13}).$

At present, there are no published studies that deal directly with the causal connection between CTE and suicide. Researchers concluded that the neuropathology of CTE caused suicidality in the initial autopsy studies, but those conclusions were premature because they were based on a small number of individuals who completed suicide. In the recently published large case series (N=85), 3 of the 33 NFL players within that series completed suicide. ¹⁹ An additional 10 of 52 former athletes completed suicide, and 6 of these 10 did not have the neuropathological features of CTE. Three of the four with CTE had stage I or stage II neuropathology (out of 4 stages of increasing severity).

At present, there is insufficient scientific evidence to conclude that there is a causal relationship between the presence of these proteinopathies and suicide in former athletes. The relevant research has simply not been performed. Several studies have been published, however, that are directly and indirectly related to this issue. Most directly and importantly, a large-scale retrospective epidemiological study of retired NFL players was undertaken to examine death rates associated with cardiovascular disease. Suicide was not a formal part of this study, but data on death by suicide were presented

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('intentional self-harm,' see table 2 in the original article). Former NFL players were *less* likely to die by suicide than men in the general population. There were only nine reported case of suicide between 1960 and 2007. Therefore, according to the only published epidemiological data until now, NFL players are at decreased risk, not increased risk, for completed suicide relative to the general population.

A large-scale survey study examined the mental health of, and experience of chronic pain in, former NFL players (3377 surveys sent with 1617 usable responses; 48.6%). ²¹ The authors reported that a minority of former players suffered from depression (approximately 15%). Approximately 25% reported chronic pain as a 'very common' problem. Depression was associated with chronic pain in these players. Moreover, those with depression, and especially those with depression and chronic pain, were significantly more likely to endorse a wide range of life concerns including occupational problems, financial problems and marital/relationship problems.

In a phone survey of 644 former NFL players, ²² 81% reported moderate or severe problems with chronic pain. When asked about prescription opioid use during their NFL playing careers, 52% reported using this medication at that time. Of those, 71% reported misusing them (eg, taking more than prescribed). Those with a history of misuse during their NFL career were significantly more likely to misuse at the present time. Specifically, 68% reported no current use, 17% reported use as prescribed and 15% reported misuse of prescription opioids during the prior 30 days. Current misuse of narcotic pain medications was significantly associated with greater levels of pain, self-reported history of undiagnosed concussions and current heavy drinking.

In a recent large survey study of retired NFL players,²³ a substantial minority admitted to a history of anabolic steroid use during their playing career; in fact, one in five players from the 1980s reported taking steroids.²³ Steroid use was associated with greater risk for musculoskeletal injuries. It was also associated with increased lifetime risk for back pain and depression. In a recently published study of retired Swedish elite male athletes, the authors reported that past steroid use was associated with increased future risk of suicide in former wrestlers, power lifters, Olympic lifters and those in track and field throwing events.²⁴ In a small prior study, a possible connection between steroid use and future suicide was reported in Finnish power lifters.²⁵

Taken together, the studies until now suggest that NFL players are less likely to die by suicide than men in the general population. However, their rate of chronic pain and opioid use is high, and their rate of depression might be somewhat elevated relative to the general population. Former NFL players with depression, and especially those with depression and chronic pain, are much more likely to report life stress and financial difficulty than former players without depression.

It is well established in the literature that patients seeking treatment for chronic pain have high rates of comorbid depression.²⁷ In the general population, the incidence of depression in those with chronic pain is somewhat elevated.^{28–30} There is also evidence that patients with chronic pain are at increased risk of suicidal ideation³¹ and of suicide.³² Therefore, without question, the literature would suggest that former athletes with life stress, financial difficulty, chronic pain and depression would be at increased risk of suicidal ideation and completed suicide.

Some unanswered questions regarding CTE

There are important unanswered questions about the modern version of CTE. First, it has not been established scientifically that this proteinopathy in the brain can cause depression, drug misuse or suicidality. Second, it is not known whether patients with depression, chronic pain and problems with drug misuse, singly or in combination, who did not play sports and have no history of repetitive neurotrauma, are at increased risk of having τ , TAR DNA-binding protein 43 (TDP-43) or β amyloid depositions in their brains. Third, it is not known whether certain genetic factors place people in their 40s through 60s at increased risk of certain proteinopathies in the presence or absence of a history of repetitive neurotrauma. Fourth, it is not known whether heart disease, diabetes or metabolic syndrome is associated with similar neuropathological findings in some people. Finally, it is not known whether a history of anabolic steroid use is associated with any of the aforementioned proteinopathies.

Lessons learnt from the large literature relating to the neuropathology of Alzheimer's disease³³ can be systematically applied to the slowly emerging literature on the correlation between CTE neuropathology and clinical features in general, and suicide in particular. For example, there is an extensive literature, spanning many years, on the correlation of Alzheimer's disease neuropathology with cognitive functioning. This body of evidence suggests that (1) many patients with early-stage neuropathological changes do not show evidence of clinical change, (2) patients with a heavy burden of neuropathology are very likely to have cognitive impairment and (3) neuropathological comorbidity is very common, and this comorbidity can influence clinical features. 33-37 In a recent review of the neuropathology of Alzheimer's disease, Nelson et al³³ wrote "There are prevalent (more than two thirds of patients) comorbidities. including cerebrovascular diseases, synucleinopathies, tauopathies, frontotemporal lobar degeneration and TDP-43-related diseases, in the brains of aged persons that inevitably skew correlations between neuropathologic findings and cognition" (page 373). This was recently found in a systematic review of 158 cases of CTE reported by Gardner et al. 38 They noted that of the 85 autopsies that have been performed in athletes over the past few years, 20% had 'pure' neuropathology consistent with CTE, 52% had CTE plus other neuropathology, 5% had neuropathology but no CTE and 24% had no neuropathology.

Risk factors for suicide

Over the past few decades, there have been thousands of published studies relating to suicide. Suicide is difficult to predict in individual cases. There are, however, many known risk factors. Although depression has long been considered the psychiatric disorder most associated with suicide, researchers have found that suicide ideation is predicted by depression—but suicide plans and attempts are more strongly associated with disorders characterised by anxiety/agitation (eg, post-traumatic stress disorder) and poor impulse control (eg, drug misuse).^{39 40} Major interpersonal stressful life events might precipitate suicide attempts in people with alcohol problems. 41 Other risk factors include childhood adversities, such as physical abuse, sexual abuse or family violence⁴²; physical illnesses⁴³; interpersonal/ family conflict⁴⁴; personality disorders³⁹; impulsivity and aggression⁴⁵ 46; and hopelessness.⁴⁷ Previous suicide attempts are a strong predictor of future completed suicide. 48 In adults over the age of 50, depression, 49 aggression, 50 limited social connectedness⁵¹ and poor physical health⁵² are associated with increased risk of suicide. In general, there is a mature body of evidence suggesting that the causes of suicide are complex, multifactorial and difficult to predict in individual cases. Therefore, researchers and clinicians are encouraged to be prudent, circumspect and critical in their approach to interpreting the strongly presented causal relationship between the proteinopathy of CTE and suicide that is discussed frequently in the media and increasingly in the published literature.

CONCLUSIONS

The initial case studies of modern CTE have shown that former athletes who died by suicide show evidence of (1) an abundance of neurofibrillary inclusions in the form of neurofibrillary tangles, neuropil threads and glial tangles; (2) β -amyloid deposits; and (3) widespread TDP-43 proteinopathy in their brain. ¹ A unique characteristic of CTE appears to be the location of the neuropathology, at the depth of sulci. Finding evidence of the neuropathology of CTE in the brains of former athletes who complete suicide is a provocative but not statistically compelling source of evidence. The putative causal link in individual cases represents circular reasoning (ie, *petitio principii*). At present, the association between the neuropathology of CTE and suicide has not satisfied basic criteria relating to the consistency, strength, temporality, specificity or coherence of the correlation. ⁵³

Future research might establish a clear causal connection between the proteinopathy of CTE, suicidal ideation, suicide attempts and/or completed suicide. At present, however, there are no cross-sectional, epidemiological or prospective studies showing a relation between concussions or subconcussive blows in contact sports and completed suicide. One epidemiological study suggests that retired NFL players have lower rates of death by suicide than the general population,²⁰ although chronic pain and depression²¹ ²² certainly could be risk factors in former athletes. The single epidemiological study, however, does not clearly address the issue of whether the neuropathology of CTE is causally related to suicide unless one assumes that the majority of former NFL players will develop CTE (which is probably a faulty assumption). If only a small minority of former NFL players develop CTE, then the relation between neuropathology and suicide could be obscured in the epidemiological study. Moreover, it is important to appreciate that suicidality has different aspects including ideation, attempts and completed suicide. The risk factors for each of these aspects of suicidality in former athletes might be different, and the relation between the neuropathology of CTE and these aspects is unknown. Given that there were only nine reported deaths by suicide in former NFL players between 1960 and 2007, 20 and there have been six reported suicides in the past 2 years, it is essential to carefully investigate the diverse range of risk factors for suicidality in former athletes—and not adopt a singular mechanistic assumption about a proteinopathy as the primary explanation.

Without question, some former athletes are at risk of suicide —and this problem is not limited to those who played contact sports. Future research is needed to determine if the risk of suicide differs among those with a history of contact versus noncontact sports. Most years, for example, a former major league baseball player commits suicide (as tracked on several websites; eg, http://www.thedeadballera.com/suicides.html). Suicide is a societal problem—a problem that affects athletes in non-contact sports, such as cricket, baseball, power lifting and track and field throwing events. 24 54-56 Clinicians should have higher levels of concern when known risk factors accumulate. For example, a person with depression, chronic pain and drug misuse, who finds himself under serious interpersonal or financial life stress, would be at increased risk of suicide. It is important to monitor for suicidality in former athletes with mental health problems. Swift, evidence-based mental health treatment will most likely reduce the risk of suicide and substantially improve the quality of life of former athletes who are suffering.

Competing interests GLI has been reimbursed by the government, professional scientific bodies and commercial organisations for discussing or presenting research relating to mild TBI and sport-related concussion at meetings, scientific conferences and symposiums. He has received research funding from several test publishing companies, including ImPACT Applications, Inc, CNS Vital Signs, and Psychological Assessment Resources (PAR, Inc). He is a co-investigator, collaborator or consultant on grants relating to mild TBI funded by several organisations, including, but not limited to, the Canadian Institute of Health Research, Alcohol Beverage Medical Research Council, Rehabilitation Research and Development (RR&D) Service of the US Department of Veterans Affairs, Vancouver Coastal Health Research Institute and Roche Diagnostics Canada.

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